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(54) Title: IMPROVED METHOD FOR SYNTHESIS

(57) Abstract

The present invention relates to an improved method for the synthesis of omeprazole, comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole with m-chloroperoxy-benzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

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Improved method for synthesis

Technical field

The present invention relates to an improved method for the synthesis of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl-1H-benizimidazole, referred to under its generic name omeprazole throughout the following specification and claims.

Prior art

US-A-4 255 431 discloses a process for the synthesis of omeprazole comprising the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole in a methylene chloride solution with m-chloroperoxybenzoic acid resulting in the formation of omeprazole and m-chlorobenzoic acid. omeprazole is highly sensitive to acids, and the reaction mixture has to be maintained at a low temperature to prevent excessive decomposition in the reaction mixture.

The product is worked-up by filtering-off of m-chlorobenzoic acid formed during the reaction. The filtrate is diluted with methylene chloride, is extracted with Na_2CO_3 solution, dried and evaporated. The resulting omeprazole product is contaminated with starting materials and by-products.

Summary of the invention

The object of the present invention is to provide an improved method for the synthesis of omeprazole, which eliminates the drawbacks of previously known methods.

This object is achieved according to the present inven-

tion, which is characterized by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl-thio]-1H-benzimidazole (below denoted Compound I) with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in crystallization of omeprazole.

The m-chloroperoxybenzoic acid is suitably used in an amount of 0.7 - 1.4 molar equivalents of Compound I, and preferably in an amount of 0.9 - 1.2 molar equivalents.

According to one embodiment of the invention, the alkyl formate is methylformate or ethylformate, methylformate being preferred.

The alkyl formate is suitably used in an amount of 1.2 - 2.0 molar equivalents of Compound I, and preferably in an amount of 1.5 - 1.8 molar equivalents.

One important feature of the method according to the invention is that unreacted sulfide is not transferred into the aqueous phase upon the extraction with aqueous NaOH. Another important feature is that m-chlorobenzoic acid does not crystallize upon the addition of methyl-formate to the aqueous phase, thereby eliminating the need of filtering-off of m-chlorobenzoic acid in a previous step.

The pH of the reaction mixture may be maintained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH or with the use of a buffer. Preferred buffers are sodium bicarbonate and potassium bicarbonate.

A great advantage of the method according to the invention is that the reaction takes place in the organic methylene chloride phase while the m-chlorobenzoic acid formed during the reaction goes into the aqueous phase containing the buffer, in the case a buffer is used. Because of this, omeprazole formed does not stay in contact with the acid and the reaction may be performed at a temperature above 0°C.

According to one embodiment of the invention the pH of the aqueous NaOH phase is kept at above about 12.

According to another embodiment of the invention the crystallization of omeprazole is performed at a pH of above 9.

The invention will be further illustrated below with a non-limiting example.

Example

5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (16.2 g; 0.0492 mol) is reacted with m-chloroperoxybenzoic acid (13.6 g; 0.0537 mol) in CH_2Cl_2 acting as a solvent at a pH of 8.6, which is maintained by the presence of $KHCO_3$ (5.6 g; 0.056 mol) acting as a buffer. The temperature is maintained at about 0°C during the addition.

Diluted NaOH is added to a pH above 12 and the CH_2Cl_2 phase is separated off.

Methylformate (4.7 g) is charged to the water phase and the pH is kept above 9, whereupon omeprazole crystallizes. The crystals are filtered off and are washed with water and methanol at a temperature of about 0°C. The washed crystals are dried under vacuum. Yield: 15.6 g (92 %).

Claims

1. An improved method for the synthesis of omeprazole, characterized by the steps of reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylthio]-1H-benzimidazole (Compound I) with m-chloroperoxybenzoic acid in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; extracting the reaction mixture with aqueous NaOH; separating the aqueous phase from the organic phase; and adding an alkyl formate to the aqueous phase, resulting in the crystallization of omeprazole.

2. Method according to claim 1, characterized in that the m-chloroperoxybenzoic acid is used in an amount of 0.7 - 1.4, preferably 0.9 - 1.2, molar equivalents of Compound I.

3. Method according to claim 1 or 2, characterized in that the alkyl formate is methylformate.

4. Method according to claims 1 - 3, characterized in that pH of the reaction mixture is maintained within the pH range of 8.0 - 8.6 with the aid of pH static titration with NaOH.

5. Method according to claims 1 - 4, characterized in that pH of the reaction mixture is maintained within the pH range of 8.0 - 8.6 with the use of a buffer.

6. Method according to claim 5, characterized in that the buffer is sodium bicarbonate or potassium bicarbonate.

7. Method according to claims 1 - 6, characterized in that the pH of the aqueous NaOH phase is

kept at above about 12.

8. Method according to claims 1 - 7, c h a r a c t e - r i z e d in that the alkyl formate is added in an amount of 1.2 - 2.0, preferably 1.5 - 1.8, molar equivalents of Compound I.

9. Method according to claims 1 - 8, c h a r a c t e - r i z e d in that the crystallization of omeprazole is performed at a pH of above 9.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00402

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 401/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US, A, 4255431 (AKTIEBOLAGET HÄSSLE) 10 March 1981, see example 1 --	1
A	US, A, 4182766 (HOFFMANN-LA-ROCHE INC) 8 January 1980, see example 17 --	1
A	WO, A1, 8705021 (AKTIEBOLAGET HÄSSLE) 27 August 1987, see example 1 --	1
A	EP, A, 0197013 (AKTIEBOLAGET HÄSSLE) 8 October 1986, see example 2 --	1

* Special categories of cited documents:[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28th August 1991	1991 -09- 10
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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A	EP, A, 0163842 (F. HOFFMANN-LA ROCHE & CO.) 11 December 1985, see example 4 -- --------	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00402

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